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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/344,676	06/25/1999	WILLIAM P. VAN ANTWERP	PD-0310	9328

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EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 03/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/344,676	VAN ANTWERP ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,8,9,11,17,19-21,59,61,62,64-66 and 71* is/are pending in the application.

4a) Of the above claim(s) *1,5,8,9,11,17,19,20,59,61,62,64-66 and 71* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Pursuant to the directives of the amendment filed 12/22/03, claims 1, 2, 5, 11, 17, 19, 21, 59, 61 have been amended, and claims 4, 6, 14, 25-52, 58, 60 cancelled. Claims 1-3, 5, 8, 9, 11, 17, 19-21, 59, 61, 62, 64-66, 71 are now pending. Claims 1, 5, 8, 9, 11, 17, 19, 20, 59, 61, 62, 64, 65, 66, 71 are withdrawn from consideration. Claims 1 and 59 are withdrawn from consideration because the elected species were such that agent (i) was chosen to be human insulin, and not an insulin analog. Similarly, claim 5 does not encompass human insulin. As for claim 20, the elected species were such that additional compounds of agent (i), (ii) or (iii) were not required.

In accordance with the foregoing, claims 2, 3 and 21 are examined in this Office action.

The response filed 12/22/03 makes no arguments as to the validity of the previously imposed §103 rejections. Accordingly, the question of whether applicants' arguments are found persuasive is rendered moot.

The term "**CMC**" is used hereinbelow as an abbreviation for "critical micellar concentration"

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Claims 2 and 3 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Each of claims 2 and 3 is dependent on a non-elected claim.

Claim 2 is dependent on claim 1; claim 1, in turn, recites that "the surfactant ... is present in an amount affording a concentration less than the CMC of said composition". The term "CMC" is not being used in a manner that is consistent with the meaning of this term as understood by the physical chemist or biochemist of ordinary skill. The term "CMC" is routinely used to describe the concentration of a *surfactant*, the concentration being that which is minimally necessary in order for the surfactant to form micelles. By contrast, claim 1 (and by incorporation, claim 2 as well) defines the surfactant concentration in terms not of the CMC of the surfactant, but rather, in terms of the CMC of the composition. What this might mean is rather unclear, when the claims are viewed in a vacuum. In reality, none of the components of the composition will form micelles anyway, apart from the surfactant itself. Certainly, the compound pioglitazone will not form micelles. Insulin will also not form micelles, although it is possible to prepare micelles which contain insulin. But even if some of the insulin is incorporated into the micelles, most of the insulin will remain outside of the micelles. As for pioglitazone, it is unlikely that this compound could be incorporated into micelles to a significant degree. Further, the most abundant compound in the composition is water. Although water is necessary for the formation of micelles, it is also true that only a very small portion of the water molecules can be said to be incorporated into the micelles. Similarly, if the composition contains inorganic ions (e.g., zinc and phosphate) or glycerin (see pages 9-12 of the specification) only a very small portion of these compounds will become incorporated into the micelles. Thus, no matter how high or how low the concentration of the surfactant, one can never get all of the components (or even most of the components) into micelles. Accordingly, making reference to the CMC of the composition, rather than the CMC of the surfactant, has no particular meaning.

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The following is a quotation of 35 USC §103 which forms the basis for all obviousness rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 2, 3 and 21 are rejected under 35 U.S.C. §103 as being unpatentable over Walter H. M. (*Diabetes Research* **13** (2) 75-7, 1990) in view of Rieveley (USP 6,153,632).

As indicated previously, Walter discloses (page 76, col 1, paragraph 2) "HOE 21 PH" insulin which is insulin combined with the surface-active stabilizer polyethylene - polypropylene glycol. Also disclosed (e.g., page 76 col 2) is that use of the "HOE 21 PH" insulin resulted in less catheter occlusion and a "significant improvement of metabolic control". Walter does not suggest combining insulin with an insulin sensitizer. Walter also does not state that the surface-active stabilizer is present "in an amount affording a concentration less than the CMC of said composition".

As indicated previously, Rieveley discloses (e.g., col 4, line 50+) a composition comprising insulin and an insulin sensitizer. As stated (col 4, line 56+), the effect of the insulin sensitizer is to sensitize the cells of the mammal so as to enhance insulin uptake and/or utilization of glucose by the cells of the mammal thus reducing the therapeutic dose

of insulin that is required. Rieveley does not teach combining insulin with the surface-active stabilizer polyethylene - polypropylene glycol.

The first issue concerns the "CMC of the composition". An analysis of this phrase is given above in the rejection under §112 second paragraph. This discussion is incorporated by reference herein. As such, reference to the CMC of the composition does not further limit the claim, since regardless of the concentration of the surfactant, the entire composition will not itself consist exclusively (or even primarily) of micelles. It is noted that the specification on page 6 (lines 18-21) implies that the phrase at issue refers to a situation in which the concentration of the surfactant is less than that which results in a two phase composition. In the event that such a qualification were to be incorporated into the claims, this ground of rejection would still be maintained. The reason would be that the drug formulation specialist of ordinary skill would prefer a homogeneous mixture to a heterogeneous one, given that the objective is subcutaneous insulin infusion.

Thus, the endocrinologist of ordinary skill would have been motivated to use the surface-active stabilizer polyethylene - polypropylene glycol in order to reduce catheter occlusion and to achieve a "significant improvement of metabolic control". The endocrinologist of ordinary skill would have been motivated to use the insulin sensitizer to enhance insulin uptake and/or utilization of glucose by the cells of the patient. Thus, by combining the

teachings of Walter and of Rieveley, the artisan of ordinary skill would arrive at the claimed composition. The claims are thus rendered obvious.

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Claims 2, 3 and 21 are rejected under 35 U.S.C. §103 as being unpatentable over Grau (*Diabetes* **36** (12) 1453-1459, 1987) in view of Rieveley (USP 6,153,632).

Grau discloses (page 1453, col 2) "HOE 21 PH" insulin which is insulin combined with the surface-active stabilizer polyethylene - polypropylene glycol. Also disclosed is that the "HOE 21 PH" reduces the precipation and catheter occlusion that would otherwise occur with insulin alone. Grau conveys that "HOE 21 PH" insulin is advantageous when used with insulin infusion pumps. Grau does not suggest combining insulin with an insulin sensitizer. Grau also does not state that the surface-active stabilizer is present "in an amount affording a concentration less than the CMC of said composition".

As indicated previously, Rieveley discloses (e.g., col 4, line 50+) a composition comprising insulin and an insulin sensitizer. As stated (col 4, line 56+), the effect of the insulin sensitizer is to sensitize the cells of the mammal so as to enhance insulin uptake and/or utilization of glucose by the cells of the mammal thus reducing the therapeutic dose of insulin that is required. Rieveley does not explicitly state that "insulin" is a peptide which is "related" to insulin, and Rieveley does not teach combining insulin with the surface-active stabilizer polyethylene - polypropylene glycol.

The arguments regarding the CMC of the composition given above (the §103 over Walter in view of Rieveley) are incorporated by reference herein.

Thus, the endocrinologist of ordinary skill would have been motivated to use the surface-active stabilizer polyethylene - polypropylene glycol in order to reduce precipitation and catheter occlusion. The endocrinologist of ordinary skill would have been motivated to use the insulin sensitizer to enhance insulin uptake and/or utilization of glucose by the cells of the patient. Thus, by combining the teachings of Grau and of Rieveley, the artisan of ordinary skill would arrive at the claimed composition. The claims are thus rendered obvious.

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Claims 2, 3 and 21 are rejected under 35 U.S.C. §103 as being unpatentable over Walter H. M. (*Diabetes Research* **13** (2) 75-7, 1990) in view of Clark (USP 5,783,556) further in view of Rieveley (USP 6,153,632).

As indicated above, Walter discloses (page 76, col 1, paragraph 2) "HOE 21 PH" insulin which is insulin combined with the surface-active stabilizer polyethylene - polypropylene glycol. Also disclosed (e.g., page 76 col 2) that use of the "HOE 21 PH" insulin resulted in less catheter occlusion and a "significant improvement of metabolic control". Walter does not suggest combining insulin with an insulin sensitizer or with IGF-I.

As indicated previously, Clark discloses a composition comprising insulin and IGF-1. It

is disclosed (e.g., col 20, line 52+) that coadministration of insulin and IGF-I leads to unexpectedly lower glucose levels, which is advantageous in the management of diabetic patients. Clark does not disclose the use of insulin sensitizers.

As indicated previously, Rieveley discloses (e.g., col 4, line 50+) a composition comprising insulin and an insulin sensitizer. As stated (col 4, line 56+), the effect of the insulin sensitizer is to sensitize the cells of the mammal so as to enhance insulin uptake and/or utilization of glucose by the cells of the mammal thus reducing the therapeutic dose of insulin that is required. Riveley does not teach combining insulin with the surface-active stabilizer polyethylene - polypropylene glycol or with IGF-I.

The arguments regarding the CMC of the composition given above (the §103 over Walter in view of Rieveley) are incorporated by reference herein.

The practitioner of the Walter invention would be in possession of a combination of insulin and polyethylene - polypropylene glycol which could be used for treatment of diabetes. The artisan of ordinary skill would take from Clark the disclosure that coadministration of insulin and IGF-I leads to unexpectedly lower glucose levels, which is advantageous in the management of diabetic patients. The artisan of ordinary skill would take from Rieveley the disclosure that by combining insulin with an insulin sensitizer, the result is that the cells of the patient will be sensitized so as to enhance insulin uptake and/or utilization of glucose by the cells of the mammal thus reducing the therapeutic dose of insulin that is required.

Accordingly, the artisan of ordinary skill would have been motivated to combine insulin with polyethylene - polypropylene glycol, amylin and an insulin sensitizer. Thus, the claims are rendered obvious.

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Claims 2, 3 and 21 are rejected under 35 U.S.C. §103 as being unpatentable over Walter H. M. (*Diabetes Research* **13** (2) 75-7, 1990) in view of Cooper (USP 5,641,744), further in view of Rieveley (USP 6,153,632).

As indicated above, Walter discloses (page 76, col 1, paragraph 2) "HOE 21 PH" insulin which is insulin combined with the surface-active stabilizer polyethylene - polypropylene glycol. Also disclosed (e.g., page 76 col 2) that use of the "HOE 21 PH" insulin resulted in less catheter occlusion and a "significant improvement of metabolic control". Walter does not suggest combining insulin with an insulin sensitizer or with amylin.

As indicated previously, Cooper discloses (e.g., col 3, line 37+) a composition comprising insulin and amylin. Cooper also discloses (col 3, line 57+) that the combination provides "tighter diabetic control with reduced risk of hypoglycemia". Cooper does not disclose the use of insulin sensitizers.

As indicated previously, Riveley discloses (e.g., col 4, line 50+) a composition comprising insulin and an insulin sensitizer. As stated (col 4, line 56+), the effect of the insulin sensitizer is to sensitize the cells of the mammal so as to enhance insulin uptake and/or

utilization of glucose by the cells of the mammal thus reducing the therapeutic dose of insulin that is required. Rieveley does not teach combining insulin with the surface-active stabilizer polyethylene - polypropylene glycol, or with amylin.

The arguments regarding the CMC of the composition given above (the §103 over Walter in view of Rieveley) are incorporated by reference herein.

The practitioner of the Walter invention would be in possession of a combination of insulin and polyethylene - polypropylene glycol which could be used for treatment of diabetes. The artisan of ordinary skill would take from Cooper the disclosure that combining insulin with amylin will produce "tighter diabetic control with reduced risk of hypoglycemia". The artisan of ordinary skill would take from Rieveley the disclosure that by combining insulin with an insulin sensitizer, the result is that the cells of the patient will be sensitized so as to enhance insulin uptake and/or utilization of glucose by the cells of the mammal thus reducing the therapeutic dose of insulin that is required.

Accordingly, the artisan of ordinary skill would have been motivated to combine insulin with polyethylene - polypropylene glycol, amylin and an insulin sensitizer. Thus, the claims are rendered obvious.

✹

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at 571-272-0951. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

D. Lukton 3/12/04

ROBERT A. WAX
PRIMARY EXAMINER